4; page 20, lines 8-12 and; page 33, lines 6-10. Applicant submits that these amendments introduce no new matter.

In addition, independent claims 1, 3, 12, 20, and 31 are amended to recite a combination of an immunoconjugate and an angiogenesis inhibitor that induces a greater response than "the immunoconjugate alone." Support for these amendments is found in the application as filed, for example, at least on page 3, lines 25, through page 4, line 4, and on page 46, lines 8-12. Applicant submits that these amendments introduce no new matter.

Claim Objection

Claim 3 was objected to. Claim 3 is hereby rewritten in independent form to overcome the objection.

35 U.S.C. § 103 Rejections

i. Claims 1-2 and 4-39 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Gillies et al. (WO 92/08495) ("Gillies") in view of O'Reilly et al. (Cell 88: 277-285 (1997)) ("O'Reilly I").

Applicant submits that the claims as amended herein are directed to a combination of an immunoconjugate and an angiogenesis inhibitor to induce a cytocidal immune response against a target cell that is greater than the response induced by the immunoconjugate alone.

According to the Office action, "it would have been obvious to the ordinary artisan at the time the invention was made to substitute the cytocidal immunoconjugate taught by Gillies et al. in any therapy involving cytotoxicity." However, Applicant respectfully submits that the "combined treatment" recited in O'Reilly I specifically refers to *Teicher et al.*, Int. J. Cancer 57, 1-6,1994 ("Teicher"). See O'Reilly I, page 282, lines 27-30. Applicant submits that Teicher reports DNA-targeting agents that produce either cross-links or strand-breaks in cellular DNA, thus resulting in cell-death.

In contrast, Applicant's claimed invention is directed to a method of inducing a cytocidal immune response against a target cell by administering a combination of an immunoconjugate and an angiogenesis inhibitor, wherein the immunoconjugate includes a cytokine that induces the immune response. Accordingly, Applicant's claimed invention relates to a combination that induces a targeted immune response rather than a combination that targets DNA.

Furthermore, there is no suggestion in Gillies or O'Reilly I that a combination of an immunoconjugate with an angiogenesis inhibitor will induce a cytocidal immune response against a target cell that is greater than the response induced by the immunoconjugate alone.

In conclusion, neither Gillies nor O'Reilly I teach, suggest, or motivate using an angiogenesis inhibitor in combination with an immunoconjugate that is capable of inducing an immune response against a target cell that is greater than the immune response induced by the immunoconjugate alone. Accordingly, Applicant submits that the Gillies and O'Reilly I were improperly combined and respectfully requests that this rejection of claims 1-2, and 4-39 under 35 U.S.C. § 103 be reconsidered and withdrawn.

ii. Claims 1, 11 and 26 were rejected under 35 U.S.C § 103(a) as being unpatentable over Gillies (WO 92/08495) in view of O'Reilly, (Cell 79: 315-328 (1994)) ("O'Reilly II") or Brooks et al. (Cell 79: 1157-1164 (1994)) ("Brooks") or Ingber et al. (Nature 348: 555-557 (1990)) ("Ingber").

As discussed above, Gillies in view of O'Reilly I does not render Applicant's claimed invention obvious to one of ordinary skill in the art. Applicant further submits that O'Reilly II, Brooks, and Ingber fail to cure the deficiencies of O'Reilly I or Gillies. Accordingly, at least for the same reasons stated above with respect to Gillies and O'Reilly I, Applicant submits that Gillies and O'Reilly II, Brooks, or Ingber were improperly combined.

Accordingly, Applicant respectfully requests that this rejection of claims 1, 11, and 26 under 35 U.S.C. § 103 be reconsidered and withdrawn.

CONCLUSION

Based on the above amendments and remarks, Applicant respectfully submits that pending claims 1-39 are in condition for allowance and request entry as such. If the Examiner believes that a conversation with Applicant's attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 248-7240.

Respectfully submitted,

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MARKED UP VERSION OF CLAIMS SHOWING AMENDMENTS

1.(Amended) A method of inducing a cytocidal immune response against a target cell [preselected cell-type], in a mammal, the method comprising:

administering to a [the] mammal a combination of (i) an immunoconjugate comprising an antibody binding site capable of binding a target antigen expressed on a target cell [the preselected cell-type] and a cytokine [capable of inducing the cytocidal immune response against the preselected cell-type], and (ii) an angiogenesis inhibitor,

wherein the combination induces a cytocidal immune response against the target cell that is greater than a response induced by the immunoconjugate alone.

2. (Amended) The method of claim 1, wherein the target cell [preselected cell-type] is a cancer cell.

3. (Amended) A method of inducing a cytocidal response against a virus-infected cell, in a mammal, the method comprising: [The method of claim 1, wherein the preselected cell-type is a virus-infected cell.]

administering to a mammal a combination of (i) an immunoconjugate comprising an antibody binding site capable of binding a target antigen expressed on a virus-infected cell and a cytokine, and (ii) an angiogenesis inhibitor,

wherein the combination induces a cytocidal immune response against the virus-infected cell that is greater than a response induced by the immunoconjugate alone.

8. (Amended) The method of claim 1, wherein the immunoconjugate is a fusion protein comprising, in an amino-terminal to carboxy-terminal direction, (i) the antibody binding site comprising an immunoglobulin variable region capable of binding a target antigen expressed on a target cell [a cell-surface antigen on the preselected cell-type], an immunoglobulin CH1 domain, an immunoglobulin CH2 domain, and (ii) the cytokine.

12. (Amended) A method of inducing a cytocidal immune response against a cancer cell in a mammal, the method comprising:

administering to a [the] mammal a combination of (i) an immunoconjugate comprising an antibody binding site capable of binding a target antigen expressed on a cancer cell [the cancer cell] and a cytokine [capable of inducing the cytocidal immune response against the cancer cell], and (ii) an angiogenesis inhibitor selected from the group consisting of endostatin and angiostatin,

wherein the combination induces a cytocidal immune response against the cancer cell that is greater than a response induced by the immunoconjugate alone.

17. (Amended) The method of claim 12, wherein the immunoconjugate is a fusion protein comprising, in an amino-terminal to carboxy-terminal direction, (i) the antibody binding site comprising an immunoglobulin variable region capable of binding a target antigen expressed on a target cell [a cell surface antigen on the preselected cell-type], an immunoglobulin CH1 domain, an immunoglobulin CH2 domain, and (ii) the cytokine.

20. (Amended) A composition for inducing an immune response against a target cell in a mammal, the composition comprising in combination:

(i) an immunoconjugate comprising an antibody binding site capable of binding a target antigen expressed on a target cell [the preselected cell-type] and a cytokine[capable of inducing an immune response against the preselected cell-type in the mammal], and (ii) an angiogenesis inhibitor,

wherein the combination induces a cytocidal immune response against the target cell that is greater than a response induced by the immunoconjugate alone.

23. (Amended) The composition of claim 20, wherein the immunoconjugate is a fusion protein comprising, in an amino-terminal to carboxy-terminal direction, (i) the antibody binding site comprising an immunoglobulin variable region capable of binding a target antigen on a target cell [a cell surface antigen on the preselected cell-type], an immunoglobulin CH1 domain, an immunoglobulin CH2 domain, and (ii) the cytokine.

27. (Amended) The composition of claim 20, wherein the target cell [preselected cell-type] is a cancer cell.

31. (Amended) A method for reducing the size of a tumor in a mammal, the method comprising:

administering to a [the] mammal (i) an immunoconjugate comprising an antibody binding site capable of binding a target antigen expressed on a target cell in [a preselected cell-type of] a tumor and a cytokine [capable of inducing a cytocidal immune response against the preselected cell-type], and (ii) an angiogenesis inhibitor[in an amount sufficient to enhance the reduction of the size of the tumor relative to the immunoconjugate alone.],

wherein the combination induces a reduction in size of the tumor that is greater than a reduction in size induced by the immunoconjugate alone.

36. (Amended) The method of claim 31, wherein the immunoconjugate is a fusion protein comprising, in an amino-terminal to carboxy-terminal direction, (i) the antibody binding site comprising an immunoglobulin variable region capable of binding a target antigen expressed on a target cell [a cell surface antigen on the preselected cell-type], an immunoglobulin CH2 domain, and (ii) the cytokine.